



Multiple Myeloma

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COURTESY OF CITIZENS SOCIETY

I. ABSTRACTMULTIPLE MYELOMA

C. M. Eklund

Multiple myeloma is a primary myeloid tumor in which multiple tumor foci arise in the red bone marrow. It is characterized by skeletal pain, spontaneous fractures, multiple tumors, Bence-Jones proteinuria, high plasma proteins and anemia. About 500 cases have been reported. Nothing is known as to etiology. Trauma is frequently cited as an inciting agent but no good evidence for this has been presented.

A. IncidenceI. Age.

Wallgren, 90% over 40 years.

Geschickter and Copeland, 80% between 40 and 70 with peak at 55.

Up to 1933, Magnus-Levy considered it doubtful if any proven case had been reported in childhood.

In 1934, Slavens collected 3 cases from the literature which he considered as definitely proven histologically and presents a case of his own - aged 4. In this case, the history, roentgenologic findings, biopsy and autopsy all pointed to multiple myeloma.

II. Sex

Various statistics agree on about 70% males.

III. Race

Reported in white, yellow and black races.

IV. Social Status

In every class of society.

V. Countries

Most cases reported from Germany and the United States but others reported

from nearly every part of the world. The greater incidence in certain places appears to be due to the greater interest shown in the disease in those places?

VI. Among malignancies, Geschickter and Copeland estimate that it comprises about 0.03% of all malignancies.

B. Presenting Symptoms and Signs

The clinical course is varied. May resemble chronic arthritis, kidney disease, severe anemia, pulmonary disease or various neurological diseases.

I. Pain usually ushers in the disease and brings the patient to the physician. The onset may be definitely associated with some sudden movement or follow lifting. The pain sometimes appears suddenly from no apparent cause. When the pain has once appeared, it is characteristically related to motion and is usually intermittent. In some, the attack of pain is so sudden and of such severity that the patient must grasp something for support. Wallgren cites a case where an attack occurred while the patient was walking down stairs, and he fell the rest of the way. Occasionally, the pain is so severe as to require general anesthesia.

The pain is usually situated in the back, especially the lumbar region. The chest and shoulders are involved frequently; the arms and legs only occasionally; typically they are free.

The pain usually lasts a few days to weeks, then the patient is more or less free until the next unguarded movement. The pain may recur spontaneously. As the disease progresses, the pain tends to become more constant. In these patients, percussion of the thorax or palpation of the abdomen or even the pressure of the stethoscope may be very painful.

The pain at first may originate in the bone itself but sooner or later it arises from pressure upon nerves.

II. A tumor may be the presenting sign. The patient feels a lump or a painful area. Occasionally, a local tumor of the mediastinum, pelvis, nasopharynx or orbit may be so large and grow so rapidly that it characterizes the clinical picture. The tumors are described as feeling elastic and giving a sensation of fluctuation. A parchment paper-like crepitation may be present. Some tumors pulsate. A tendency to spontaneous disappearance has been described.

III. The softening and compression of the vertebrae may give a characteristic deformity. The sternum sinks in, the abdomen protrudes, the ribs rest upon the pelvis, the head sinks forward, the shoulders are braced back, the feet are placed far apart and the patient walks with deliberation. A shortening of the body up to 20 cm. has occurred.

IV. Fractures are reported in 62% of the cases (Geschickter and Copeland). While they are very common and frequently multiple, they are usually not the presenting sign. Crushing of vertebrae, following lifting, has been noted in some of the cases here. The fractures usually involve the ribs. Fracture of the femur or humerus is fairly common.

V. The majority of the patients show some neurological symptoms. Paraplegia is the most important. Diplopia, paralysis of the hand, partial laryngeal and pharyngeal paralysis have been reported. Intercostal neuralgia and root pains are quite common.

VI. Thrombosis of the intracranial sinus due to pressure of tumors has been reported a few times.

Thrombosis of the central artery of the retina - once.

Thrombosis of the retinal vein - once.

One case presented signs of vascular disturbance resembling Raynaud's disease.

VII. Some cases present themselves with only general signs such as weakness, weight loss and poor appetite.

C. Duration of the Disease

The disease is very insidious in its onset so that no accurate knowledge can be had as to its duration. Average duration is about 2 years. Proven cases reported with a duration of over 5 years. Magnus-Levy believes that the clinical course is probably much greater than is usually stated.

D. Occurrence of Amyloid

Magnus-Levy reports 37 instances in less than 150 cases of multiple myeloma. It tends to have an unusual distribution. Large masses may occur in bones or striated muscle. The intestines, heart and lungs may be infiltrated with amyloid and produce symptoms complicating the clinical picture.

E. Laboratory Findings

I. Hematology

a. Hemoglobin and red blood cells

The predominate picture is one of anemia. In 70 cases, the red blood cells were over four million in only 23% of the cases (Geschickter and Copeland). In the greater number the red blood count is between two and three million. Twenty-six of the above 70 had a high color index.

Wallgren also states that the anemia is not the usual secondary type.

Normoblasts are occasionally seen and megaloblasts have been reported a few times.

b. White blood cells. (Geschickter and Copeland)

Seventy percent (100 cases) were within normal limits, 23% showed a leucocytosis and 7% a leukopenia.

In the cases with leucocytosis, the white blood cells were usually 11,000 to 15,000.

The highest count in definitely proven cases was 39,400. This is in contrast to metastatic malignancy in which counts as high as 120,000 have been reported (Wallgren).

c. Blood Smear

In "about 60 cases," there were 15 with myelocytes (1 - 10%) (Geschickter and Copeland). Wallgren states that myelocytes do not usually exceed 2%. Geschickter and Copeland quote Vaughn as reporting myelocytes frequently present in advanced carcinoma. Myeloma cells have been found in the blood smear in a small number of cases.

d. Plasma Proteins

The great interest shown in this comparatively rare disease at the present time is due to the unusual disturbance in protein metabolism. This disturbance is revealed in 3 ways.

1. Increased plasma protein.
2. Bence-Jones protein in the urine.
3. Formation of amyloid deposits.

A marked increase in plasma protein is an uncommon laboratory finding. It is shown more strikingly in multiple myeloma than in any other disease. What percentage of cases of multiple myeloma show an increased plasma protein is unknown because plasma protein determinations have been done in only a few of the reported cases.

In 1933, Magnus-Levy collected 36 cases; 21 of these had plasma proteins of more than 8 grams per 100 cc. The proteins were not fractionated in all these cases. In most cases the increase in proteins is due to an increase in the euglobulin fraction. In some cases, it is due to increase of the pseudoglobulin fractions. Frequently fibrinogen is increased. Some cases have a normal plasma protein level; in other cases, the level may be low.

Normal Levels:

Total protein	- 7.0	(6.0-7.0)
Globulin	- 2.0	(1.4-3.0)
		(Peter & Eisenmon)
Albumin	- 5.0	(4.0-5.5)

Total plasma protein in multiple myeloma may reach 16 gms. per 100 cc.

A number of hematological and chemical peculiarities of the blood appear to be due to the increase of euglobulin.

(a) Autohemagglutination:

Reimann was the first to recognize the relation between autohemagglutination and high plasma protein in multiple myeloma. It may be impossible to do a red blood count because of the rapid clumping of the cells. It is shown in blood smears by marked rouleaux formation. Cross-matching of blood for blood transfusions may be very difficult because the patient's serum clumps red blood cells from any group. This marked rouleaux formation may account for the rapid blood sedimentation in some cases of multiple myeloma. Foord reports one case of intravascular clumping visible upon fundus examination after applying pressure to the eyeball to slow the circulation.

(b) Presence of cloudiness, precipitation or coagulation when the serum is inactivated in carrying out the Wassermann reaction.

(c) Increase in viscosity of the serum.

(d) Spontaneous precipitation of protein from the blood.

Wintrabe and Buell, while doing a hematocrit determination noticed a large amount of precipitate settle out above the red blood cells and they showed that it consisted of protein.

Gros presents a case where the increase of the protein was due to pseudo-globulin and the above changes were absent.

Jacobson reports the formation of a white precipitate on the

addition of Hayem's solution in counting red blood cells. He found that this was due to the mercury bichloride. It occurred in 3 cases in which the increase of protein was chiefly in the euglobulin fraction and it was absent in a case where the increase was due to pseudo-globulin.

Bing reports a positive formal-gel reaction. This has been used for the diagnosis of kala azar and depends upon increased globulin. Two drops of 30% formalin are added to 1 cc. serum and in positive cases a gel is formed in 1 to 5 minutes; in negative cases, no gel is formed in 3 to 24 hours.

Gros tried the Tohato-ara reaction in a case with high protein and found it positive. This test also depends upon a high globulin content.

Magnus-Levy has collected 5 cases of serum which were anticomplementary in the Wassermann test. Whether this has any relation to the high protein content is not known.

(e) Blood Chemistry

The blood calcium may be very high and is exceeded only by hyperparathyroidism. The blood phosphorus is normal or slightly elevated.

II. Urine

The striking finding is the Bence-Jones protein.

Magnus-Levy estimates its frequency in multiple myelomas at 80%.

Geschickter and Copeland report it present in 65% of their collected cases.

Bence-Jones protein is found in cases other than multiple myeloma. With 2 exceptions these have been diseases affecting bone or bone marrow. (Leukemias, bone tumors, rib and osteomalacia, caries of bone, etc.) Geschickter and Copeland were able to collect 27 such cases. The 2 exceptions mentioned were: a carcinoma of the stomach and a lympho-

sarcoma of the colon where no evidence of involvement of bones was said to have been found. Magnus-Levy estimates that 90% of all cases of Bence-Jones proteinuria are due to multiple myeloma, 3 to 5% due to leukemias.

In the classical cases of Bence-Jones proteinuria, a cloudiness appears when the urine is heated to a little above 40° and complete flocculation takes place between 50 and 60°. On boiling, the precipitate disappears and it reappears on cooling. Unfortunately, in many cases of Bence-Jones proteinuria, the precipitate does not disappear on boiling in the ordinary acetic acid test because the above phenomenon is dependent upon the hydrogen ion and salt concentration and also upon the volume of the ion present.

The following method of Osgood and Hoskins is better than heating after acidification with acetic acid:

To 5 cc. urine add 1 cc. 50% acetic acid and 3 cc. saturated Na Cl solution. A precipitate appears if Bence-Jones protein is present. The precipitate is centrifuged down, dissolved in 5 cc. of water and the reagents again added and the solution heated.

An output of 77 grams of Bence-Jones protein in one day has been reported with a protein concentration of 7.5% in an individual urine specimen (up to 7% in a days urine). A normal person has a concentration of about 7% protein in the blood stream and a total of about 300 grams blood protein.

Bence-Jones protein has been occasionally reported in large amounts in the blood plasma but Magnus-Levy doubts this and says he cannot demonstrate any Bence-Jones protein in the blood serum.

Bence-Jones protein may occur in the urine alone or in combination with plasma-protein. When plasma protein occurs it is due to some kidney lesion. Bence-Jones protein can be passed through the kidneys for years in some cases with no apparent kidney damage and is usually

not accompanied by casts or blood cells.

Geschickter and Copeland report evidence of some kidney disease in 70% of cases.

Bell studied renal changes in multiple myeloma and concluded that renal insufficiency developed frequently, especially in an advanced state of the disease. In some, it is due to arteriosclerosis, others to pyelonephritis from compression of the spinal cord or from prostatic hypertrophy. It may be due to the multiple myeloma itself in two ways:

1. Formation of tubular casts of Bence-Jones protein that obstruct the tubules and cause tubular atrophy. This may be extreme enough to cause renal insufficiency.
2. In one case, renal insufficiency was apparently caused by accumulation of high concentration of protein in the glomerular capillaries and so plugging them.

F. Pathology

Grossly, multiple myeloma is characterized by multiple tumors, most frequent in spine, ribs, sternum, skull, clavicle, upper ends of femur and pelvis, approximately in order named. The disease usually involves several bones. Only 6 cases have been reported where a single focus was found and not all of these have been followed long enough to rule out other foci or had an autopsy examination. The size of the tumors vary from those just visible to those the size of an orange. In some cases, there is no evidence of tumor formation but a diffuse involvement. The color of the tumor varies from gray to red and is gelatinous in consistence.

G. Microscopically

The tumors are not sharply demarcated. The edges are poorly defined.

Five cell types have been described.

- I. Lymphocytic type.
- II. Plasma cell type.
- III. Myelocytic type.
- IV. Myeloblastic type.
- V. Erythroblastic type.

Wallgren and others have pointed out that it is difficult to differentiate the tumor into the various types. Most appear to be classified either as the plasma cell type or myeloblastic (myelocytic) types, and in his own series he was not able to definitely place the cases in other types. Geschickter and Copeland also pointed out similar difficulties in their series. In 2 cases studied, Ewing used the term "myeloblastic" or "megaloblastic" types and Bloodgood used the term "plasma cell" type. Wallgren suggested that the term "myeloma cell" be used. All appeared to agree that the cells arise from the blood forming cells of the bone marrow.

Tumor masses in the internal organs have been found and these have the same structure as those in the marrow. The lymph glands, liver, spleen and tonsils are affected in the order named. The other organs are affected only very rarely. Not all hold to the view that these are metastases from the bone marrow. They suggest that they arise from the hematopoietic tissue present in these organs.

The question as to the development of multiple tumors is still being debated. Multiple primary tumors or metastases?

H. Diagnosis

- I. Clinical course -- skeletal pain, deformity, tumors.
- II. Blood findings -- difficulty in performing red blood counts. Wassermann test or cross matchings; non-retractile clot; rarely abnormal cells.

- III. Bence-Jones proteinuria.
- IV. X-ray -- punched out areas in spine, ribs, skull, and less characteristic findings or diffuse rarefactions.
- V. Exclusion of other conditions with similar bone lesions such as:
- a. Metastatic malignancy from:
 1. Breast
 2. Prostate
 3. Thyroid
 4. Stomach
 5. Lungs
 6. Adrenals
 7. Kidneys
 8. Ovary, uterus, pancreas and rest of intestinal tract.

Above tumors metastasize for the most part to bones which are the most frequent site of multiple myeloma.
 - b. Hyperparathyroidism.
 - c. Multiple endotheliomata.
 - d. Leukemias.
 - e. Osteomalacia.
- VI. The final diagnosis must be by biopsy since none of the findings recorded are found only in multiple myeloma.

I. Treatment

Palliation with deep x-ray.

Multiple Myeloma

1. Consists of multiple primary tumors of the red bone marrow.
2. 70% males.
3. Most between ages of 40 and 70.
4. Spine, ribs, pelvis, femurs and skull most frequently affected.

5. Clinical course characterized by pain, tumors, deformity, neurological symptoms and spontaneous fractures.
6. High blood proteins, with its manifestations.
7. Bence-Jones proteinuria - 70% of cases.
8. High frequency of renal insufficiency.
9. Amyloidosis quite common.
10. Duration about 2 years in average case.

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II. CASE REPORT

1-15-34, 43 year old
Norwegian housewife.

1-1-34 - Cough, producing small
amount of greenish, tenacious sputum.
Aching and soreness of joints and
muscles, lasted one week, and then sub-
sided.

Pain

1-15-34 - Experienced sudden severe
deep lancinating pain across back and
chest causing her to cry out. Knees
and hips became sore. Walking was diffi-
cult.

Albuminuria

2- -34 - Very difficult to walk.
Chest and back pain worse. Local
physician called. Patient understood
"kidneys were bad."

5- -34 - Unable to walk without
aid.

7- -34 - Admitted to University of
Minnesota Hospitals. Other significant
point in history: pneumonia followed by
empyema and open drainage in 1907; scar-
let fever in 1911; operated on in 1926
for prolapsed uterus two years after
last delivery. Married 18 years. Two
healthy children, 17 and 13.

Physical examination

Moderately obese, drowsy, dehydrated
and at times irrational. Occasionally,
would cry out because of shooting pains
in chest and back. Skull, ears, eyes,
nose - normal. Chest - numerour localized
areas of tenderness over ribs, most mark-
ed over 7th rib on left; few rales at
both bases, posteriorly. Heart - normal;
blood pressure 120/64 on several occa-
sions; breasts - normal. Considerable
tenderness over 8th dorsal and lower
lumbar vertebrae. Abdomen - normal.
Pelvis normal. Neurological examination -
negative.

Laboratory

X-ray plates of spine, pelvis and
chest - numerous punched out areas of
bone destruction suggestive of osteo-
clastic metastasis commonly seen in
carcinoma of breast.

When it was noted that oxalated
blood drawn for chemical study spon-
taneously formed macroscopic clumps,
giving it a very granular appearance,
hyperproteinemia was suggested and that
the most likely diagnosis was multiple
myeloma.

Urine: 24 hour volume varied from
800 to 1500 cc., usually acid; specific
gravity 1.010 to 1.018; albumin varied
from + to +++; no sugar; numerous
hyaline casts and granular casts; few
red blood cells and moderate number of
pus cells.

Blood: Hemoglobin 37%, red blood count 1,500,000 to 2,100,000, white blood cells 11,300 to 12,300, 73% granulocytes, 24% lymphocytes, 2% eosinophils, and 1% monocytes. N.P.N. 77.4 mg. %. Serum calcium - 17.3 mgs. %. Phosphorus - 6.6 mgs. %. Serum calcium 17.3 mgs. %. Phosphorus - 6.6 mgs. %. Blood proteins:

	<u>Plasma</u>	<u>Urine</u>
Fibrinogen	0.33	0.17
Euglobulin	10.20	0.30
Other globulins	1.48	0.22
Albumin	<u>1.52</u>	<u>0.38</u>
Total protein	13.53	1.07

<u>Sedimentation velocity</u>	<u>Patient's serum + Patient's cells</u>	<u>Patient's serum + Normal washed cells</u>	<u>Normal serum + Patient's washed cells</u>
after 10 minutes	125	10	1
20 "	140		3
30 "	145	45	6
60 "	149	51	16
120 "	150	51	
	Spontaneous Rouleaux Formation	Rouleaux Formation	No Rouleaux Formation

Viscosity (Hess) - 7.2

No Bence-Jones protein could be found in either the urine, blood serum or plasma. Congo red test 92% dye retained in the serum at end of one hour.

The patient gradually developed uremia, the nonprotein nitrogen reaching 134.6 mgs. % and she died from a terminal bronchopneumonia.

Autopsy (Dr. A. Blumstein)

Body is well developed, somewhat obese, white female, 43 years of age, measuring about 158 cm. in length and weighing about 150 lbs. Slight rigor and hypostasis present. No edema, jaundice or cyanosis. Pupils are equal, each measuring about 5 mm. in diameter.

Peritoneal Cavity contains no excess fluid or exudate. No exudate about Appendix.

Pleural Cavities contain no excess fluid. Base of right lung is firmly adherent to diaphragm.

Pericardial Sac normal.

Heart weighs 250 grams. No vegetations

on valves. No areas of softening or fibrosis. Root of Aorta is without note. Coronaries soft and patent.

Right Lung weighs 600 grams and shows no palpable nodules. No pus can be expressed from the bronchi. Left Lung weighs 700 grams. Cut surface is somewhat mottled. Scattered areas in lung which feel very firm. Some pus can be expressed from the bronchi.

Spleen weighs 125 grams.

Liver weighs 1500 grams and shows no nodules or congestion.

Gallbladder is small and contracted, and contains a number of stones.

Gastro-Intestinal Tract shows only postmortem change.

Pancreas, Adrenals - negative.

Right Kidney weighs 175 grams, Left same. Left kidney is sent to Dr. Bell for special study. Capsule of right kidney strips easily. No excessive pitting. Pelvis is not dilated or injected.

Dr. E. T. Bell, Department of Pathology, (verbal comment): The Uremia is the result of tubules being blocked by casts of precipitated protein with resulting atrophy of the cortex. No amyloid present in the kidney.

Bladder mucosa, Genital Organs - negative.

Head: There is an area in the left occipital region about 1.5 cm. in diameter, which has a bluish tinge and feels somewhat soft and contains tumor. Examination of the brain shows no hemorrhage or tumors.

Bones: The vertebrae are unusually soft and can be readily cut. The ribs are very friable.

Diagnosis:

1. Multiple myeloma
2. Bronchopneumonia
3. Uremia
4. Cholecystitis and cholelithiasis.

III. LAST WEEK

Date: Jan. 23, 1936

Place: Recreation Room,
Nurses' Hall

Time: 12:15 to 1:25

Program: Movie: Electro-Statics
Surgical Treatment of
Hypertension.
Movie: Technique of Surgical
Treatment of Hypertension.

Present: 127

Discussion: Dr. A. W. Adson

IV. EXHIBIT

The American Society for the Control of Cancer has loaned us its traveling exhibit for the next two weeks. This particular unit is making the circuit of the mid-western medical schools and came to us from the University of

Iowa. It is being shown through the courtesy of Dr. F. L. Rector, regional representative of the Society. From this room it will be moved to various places in the medical group.

V. MOVIE

- Title: 1. Olympic Winter Sports Capital
(Elliott Film Exchange)
2. Symphony in Sight
(Universal)

VI. GOSSIP

Fifteen years ago a group of our part-time clinical men organized the Nicollet Clinic. The idea received considerable comment both pro and con. As the years have gone by various men have left the Clinic and others have come. Young men have been trained there and gone into practice for themselves, often with great credit to all. Many of the things which the Clinic was suspected of doing in the way of self-advancement proved to be groundless rumors. Through it all, there was a rare idealism. Last Saturday night the Clinic celebrated its 15th anniversary by asking their friends to come and have dinner with them at the Radisson Hotel. Fred Snyder of the Board of Regents, and Walter Biering of Des Moines, spoke. Dr. White introduced Dr. Litzenberg, who presided. It dawned on everyone as a very pleasant reaction that the Nicollet Clinic through all these years has pursued a very definite policy of "live and let live." It has never tried to take advantage of any situation where the interests of an individual were at stake. Group medicine is an "idea," the motive which has animated the Nicollet Clinic group has been "idealism.".....Sunday was the coldest Sunday of the year - also an all-time record for testing prospective blood donors in the laboratory, with 103 patients grouped and matched during the day, not to mention the necessary Kline's on the acceptable persons.....
...Dr. Frank Lahey of Boston, is expected at the staff meeting next week. The invitation was extended through the

Minneapolis Surgical Society, his host
 on Thursday of next week.....Accidents
 are either first or second as the cause
 of death from the age of 5 to 25. Thirty
 five thousand deaths are the result of
 automobile accidents and 35,000 the re-
 sult of accidents in the home. Progress
 in preventing accidents and saving lives
 is greatest in the schools and industry..
We learn that Henry E. Michelson
 made the first correct and complete de-
 scription in English of the primary
 tuberculosis complex in the skin.....
 ..Did you notice Dr. Reimann's "first"
 contribution in today's bulletin?.....A
 medical motion picture theater has been
 started for the interns and fellows.
 The next showing will be Wednesday at
 7:15 p.m. - place to be announced. A
 film on cholecystectomy with explanatory
 remarks by Wallace Ritchie, and the film
 on empyema with remarks by Herbert Carlson
 will make up the program. All interested
 are invited.....If "Who's Who" is an
 accurate guide, it takes 48,000 laborers
 to produce one son good enough to be in-
 cluded in the list, while 20 preachers
 are all that are needed to produce their
 representative. Farmers are next with
 800 men for each product.....Psycho-
 pathic Hospital maintenace failed to
 pass in a special session of the Legis-
 lature. For various reasons it was con-
 sidered not an emergency matter. Every
 effort was made to give it priority under
 special business, and this was almost
 successful. We owe special credit to our
 representatives for the splendid battle
 they made for our new unit....."Sherm"
 Sherman, former hospital steward, is back
 in Minneapolis as a representative of a
 rubber goods concern. Although we all may
 have our talents, no one has yet been
 able to take out his false teeth and make
 a speech like "Sherm.".....It would be
 well for all of us to study Dr. Adson's
 technique in presenting his material. It
 is said of him that he never fails - no
 matter what his subject or who his
 audience.....Do not forget Dr. Wangen-
 steen's lecture tomorrow evening in
 Northrop Memorial Auditorium.

Adios.